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To: EXAMINER
CHRISTINE E. FOSTER

Date: 6/7/10

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Telephone No.:

From: ALEXANDER T. STEIN ph-D.
TRASKBRITT, P.C.
REG. NO. 66,296

Message/Comments:

RE: 10/527,662
TELEPHONE INTERVIEW

Faxed by: GRADYEL Date: 6/7/10 Time: 12:27pm

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Applicant Initiated Interview Request Form

Application No.: 10/527,662 First Named Applicant: Joel S. Vanderkerckhove
Examiner: Christine E. Foster Art Unit: 1641 Status of Application: Rejection mailed

Tentative Participants:
(1) Alexander T. Stein, Ph.D. (2) Christine E. Foster
(3) _____ (4) _____

Proposed Date of Interview: Wednesday, June 9, 2010 **Proposed Time:** 3:00 EST **(AM/PM)**

Type of Interview Requested:
(1) [X] Telephonic (2) [ ] Personal (3) [ ] Video Conference

Exhibit To Be Shown or Demonstrated: [x] YES [ ] NO
If yes, provide brief description: DRAFT Amendment

Issues To Be Discussed

Issues (Rej., Obj., etc)	Claims/ Fig. #s Claims	Prior Art	Discussed	Agreed	Not Agreed
(1) 112, 1st p	1-7; 13-15		[ ]	[ ]	[ ]
(2) 112m 2nd p	1-7; 13-15		[ ]	[ ]	[ ]
(3) 102	16	Creighton; Cruikshank	[ ]	[ ]	[ ]
(4) 103	1-7; 13-15	see Continuation Sheet	[ ]	[ ]	[ ]

[ ] Continuation Sheet Attached

Brief Description of Arguments to be Presented:
See Continuation Sheet

An interview was conducted on the above-identified application on _____.
NOTE: This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).
This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advised to file a statement of the substance of this interview (37 CFR 1.133(b)) as soon as possible.

Applicant/Applicant's Representative Signature

Examiner/SPE Signature

Alexander T. Stein, Ph.D.
Typed/Printed Name of Applicant or Representative

66,296
Registration Number, if applicable

Applicant Initiated Telephonic Interview Request Form Continuation Sheet

Application No.: 10/527,662
First Named Applicant: Joel S. Vanderkerckhove
Examiner: Christine E. Foster
Tentative Participants: Alexander Stein & Christine Foster
Art Unit: 1641
Status: Non-final Rejection Mailed
Proposed Date and Time of Interview: Wednesday, June 9, 2010; 3:00 PM EST

Brief Description of Arguments to be Presented:

With respect to the rejection under the written description requirement of 35 U.S.C. §112, first paragraph, the applicants propose to amend the claims to remove the element, "wherein said compound does not interact with the majority of said proteins and/or peptides." Applicants generally submit that isolation methods of the invention should not be required to specifically identify by structure the targets of the isolation methods, for at least the reason that identification of unknown targets may be a utility of such methods; *i.e.*, the claims are drawn to a genus of methods involving isolation of compounds, and not a genus of compounds, *per se*. However, the applicants respectfully submit the proposed amendments overcome the recent written description rejection.

The applicants respectfully submit the presently proposed amendments also overcome the recent rejection under 35 U.S.C. §112, second paragraph. It is believed that removal of the element, "wherein said compound does not interact with the majority of said proteins and/or peptides," removes any indefiniteness that existed in the previously presented claims due to the asserted dependence of the compounds used in the methods on the composition of the complex mixtures also used.

Claims 1-7 and 13-15 stand rejected under 35 U.S.C. §§102(b) and 103(a) over either Creighton and Cruikshank (individually), or Creighton, Aebersold, Beals, Sahasrabudhe, Change, and GE Healthcare (in particular combinations). With respect to these rejections, the applicants' position is respectfully set forth in detail in the attached DRAFT AMENDMENT. In general, the applicants respectfully submit that the Office is employing a broad definition of "specific interaction" that is not consistent with the more particular definition that is used throughout the Specification , and which is common term of art in biochemistry that would have been recognized and understood by one of skill in the art. However, the applicants have

Applicant Initiated Telephonic Interview Request Form Continuation Sheet

generally modified the claims to include and depend from new claim 17. This claim recites, *inter alia*, that "the specificity of the interaction between the molecule and the protein or peptide in each molecule-interaction partner complex is determined by secondary or tertiary structure of the protein or peptide." Support for this claim element is provided throughout the as-filed Specification, for example, at pages 4-7. The applicants respectfully submit that at least this element removes the present claims far from the subject matter of the cited references, because those elements only contemplate the use of reagents that modify all amino acids in all proteins and/or peptides that comprise a certain reactive group.

A listing of the claims, with proposed amendments, is provided in the attached DRAFT AMENDMENT.

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Vandekerckhove et al

Serial No.: 10/527,662

Filed: March 11, 2005

For: A METHOD FOR THE IDENTIFICATION OF DRUG TARGETS

Examiner: C. Foster

Group Art Unit: 1641

Attorney Docket No.: 2676-9863US

NOTICE OF EXPRESS MAILING

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DRAFT AMENDMENT
-FOR DISCUSSION PURPOSES ONLY-

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Responsive to the Office Action of February 22, 2010, please amend the referenced patent application as follows:

Amendments to the Claims are set forth in the listing of the claims that begins on page 2 of this paper; and

Remarks start at page 7 of this paper.

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

IN THE CLAIMS:

Claims 8-12 were previously cancelled. Claims 1, 6, 7, 15, and 16 are cancelled herein. Claims 2-5, 13, and 14 have been amended herein. New claims 17-27 have been added. All of the pending claims are presented below. This listing of claims will replace all prior versions and listings of claims in the application. Please enter these claims as amended.

Listing of the Claims:

1. (Cancelled).

2. (Currently amended) The method according to claim ~~1~~ 17, wherein said complex mixture ~~of~~ comprising proteins and/or peptides is a complex mixture of proteins.

3. (Currently amended) The method according to claim 2, further comprising the cleavage of said complex mixture ~~of~~ comprising proteins into a protein peptide mixture before performing ~~step (b)~~ the first chromatographic step.

4. (Currently amended) The method according to claim ~~1~~ 17, wherein said complex mixture ~~of~~ comprising proteins and/or peptides is a protein peptide mixture.

5. (Currently amended) The method according to claim ~~1~~ 17, further comprising ~~the step of~~ identifying the at least one interaction partner.

6.-12. (Cancelled).

13. (Currently amended) The method according to claim ~~1~~ 17, wherein the compound is a drug, a drug in development, a drug lead, a drug analogue, or a drug derivative.

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

14. (Currently amended) The method according to claim ~~1~~ 17, wherein ~~the~~ multiple non-neighboring fractions ~~of the primary~~ obtained from the first chromatographic ~~separation obtained in~~ step ~~(b)~~ are pooled prior to the second chromatographic step ~~to combine a plurality of said fractions having distinct elution times into a plurality of pooled fractions, prior to the second chromatographic step~~.

15.-16. (Canceled).

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

17. (New) A method of isolating in a fraction at least one interaction partner of a molecule out of a complex mixture comprising proteins and/or peptides, wherein the molecule forms a molecule-interaction partner complex with at least one of the proteins and/or peptides in the complex mixture, the method comprising:

admixing a plurality of the molecules with the complex mixture, wherein each molecule is capable of specifically and stably interacting with a protein or peptide therein to form molecule-interaction partner complexes, wherein molecules thereof do interact with a protein or peptide to form molecule-interaction partner complexes therein, and wherein the specificity of the interaction between the molecule and the protein or peptide in each molecule-interaction partner complex is determined by secondary or tertiary structure of the protein or peptide;

separating the resulting admixture into multiple fractions in a first chromatographic step, wherein proteins and/or peptides and molecule-interaction partner complexes are present in a first fraction obtained from the first chromatographic step;

chemically and/or enzymatically altering in the first fraction or another fraction obtained from the first chromatographic step, the molecule present in at least one molecule-interaction partner complex to form at least one altered molecule-interaction partner complex; and

separating at least one fraction comprising at least one altered molecule-interaction partner complex in a second chromatographic step, wherein the first and second chromatographic steps are performed with the same or a substantially similar type of chromatography, and

wherein the at least one altered molecule-interaction partner complex elutes at a different elution time than does the same non-altered molecule-interaction partner complex in the second chromatographic separation, thereby isolating, in a fraction, at least one interaction partner of the molecule.

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

18. (New) The method according to claim 17, wherein the molecule comprises a chemically reactive group by which the molecule and the protein or peptide in each molecule-interaction partner complex may be cross-linked, wherein the molecule comprises a chemical structure by which the molecule interacts with the protein or peptide in each molecule-interaction partner complex, and wherein the chemically reactive group and the chemical structure are different.

19. (New) The method according to claim 17, wherein the secondary or tertiary structure of the protein or peptide that determines the specificity of the interaction between the molecule and the protein or peptide is unknown.

20. (New) The method according to claim 17, wherein the at least one protein and/or peptide can only form molecule-interaction partner complexes with the molecule when the at least one protein and/or peptide are in a particular conformation.

21. (New) The method according to claim 13, wherein the drug, drug in development, drug lead, drug analogue, or drug derivative specifically and stably interacts with at least one of the proteins and/or peptides at a concentration of the drug, drug in development, drug lead, drug analogue, or drug derivative that provides a therapeutic effect to a subject.

22. (New) The method according to claim 5, wherein identifying at least one interaction partner is performed using a method selected from the group consisting of mass spectrometry, electrophoresis, activity measurement, immunochemistry, and Edman sequencing.

23. (New) The method according to claim 22, wherein identifying at least one interaction partner is performed using mass spectrometry selected from the group consisting of tandem mass spectrometry and Post-Source Decay analysis.

24. (New) The method according to claim 5, wherein identifying at least one interaction partner is performed by a method comprising measuring the mass of the at least one interaction partner.

25. (New) The method according to claim 17, wherein the complex mixture comprising proteins and/or peptides is selected from the group consisting of cell lysates, microsomal fractions, cell fractions, tissues, organelles, urine, sputum, saliva, synovial fluid, nipple aspiration fluid, amnion fluid, blood, cerebrospinal fluid, tears, ejaculate, serum, pleural fluid, ascites fluid, stool, and biopsy samples.

26. (New) The method according to claim 17, further comprising treating the complex mixture comprising proteins and/or peptides to remove contaminants prior to admixing the plurality of the molecules with the complex mixture.

27. (New) The method according to claim 5, further comprising identifying the interaction site within the at least one interaction partner.

DRAFT AMENDMENT- FOR DISCUSSION PURPOSES ONLY

REMARKS

This **Draft Amendment** is being submitted for use at the telephone interview scheduled with the Examiner on Wednesday, June 9, 2010, at 3:00 pm EST.

The Office Action of February 22, 2010, has been received and reviewed. Claims 1-7 and 13-16 stand rejected. This application is to be amended as previously set forth. All claim cancellations and amendments are made without prejudice or disclaimer. Basis for the amendments, and for new claims 17-27, can be found throughout the published PCT application (WO 2004/025243), for example, in the original claims, and in the Specification, *e.g.*, at pages 4-7; page 12; pages 14-15; page 22; the several Examples; and **Table 1**. No new matter has been presented. Reconsideration is respectfully requested.

35 U.S.C. §112, first paragraph

Claims 1-7 and 13-15 stand rejected under 35 U.S.C. §112, first paragraph, for assertedly failing to comply with the written description requirement. Office Action of February 22, 2010, at page 2. Specifically, the Office asserts that, while the Specification "discloses a number of species that would apparently interact only with a minority of peptides in certain complex mixtures," the Specification "does not adequately describe the genus of compounds having this property since it is not disclosed what structural features common to the genus are responsible for function." Id., at page 4. Moreover, the Office asserts that "the claimed 'complex mixture' would encompass mixtures of varying compositions. As such, it is reasonable to assume that a compound might interact with a minority of the proteins and/or peptides in some complex mixtures, while interacting with the majority in other complex mixtures." Id., at page 5. Claims 1, 6, 7, and 15 have been cancelled herein, rendering the rejection of these claims moot. Applicants respond further as follows.

Without agreeing that the language of the previously presented claims was not adequately described (*e.g.*, the applicants do not agree one of skill in the art would not have known the applicants were in possession of isolation methods utilizing a binding compound that does not interact with the majority of molecules, proteins, or peptides in a mixture), the applicants have cancelled claim 1, and added claim 17. New claim 17, from which amended claims 2-5, 13, and 14 depend, does not recite, "wherein said compound does not interact with the majority of said

proteins and/or peptides." Description of the claimed subject matter is no longer dependent upon the assertedly unknown composition of specific complex mixtures. Thus, the applicants respectfully submit the rationale for the Office's rejection of claims 2-7, 13, and 14 should be inapplicable at least with respect to the amended claims. For at least the foregoing reasons, the applicants respectfully request the rejection of claims 2-7, 13, and 14 under 35 U.S.C. §112, first paragraph, be withdrawn.

In general, the applicants respectfully assert that the rationale underlying both of the present rejections under 35 U.S.C. §112, first paragraph, and 35 U.S.C. §112, second paragraph, is inapposite. In particular, the presently claimed methods are drawn to methods of isolating an interaction partner from a complex mixture. Through these rejections, the Office seems to suggest that the applicants must provide a precise description *of the binding partner* to describe the claimed methods. This is in contravention of one clear utility of at least some claim embodiments; *e.g.*, that the methods may be used when the binding partner is unknown prior to its isolation. It is the property of stable and selective molecule binding that defines interaction partners in complex mixtures according to the claim, which property is at least in part identified in particular proteins and/or peptides by practice of claimed methods.

35 U.S.C. §112, second paragraph

Claims 1-7 and 13-15 stand rejected under 35 U.S.C. §112, second paragraph, for assertedly being indefinite. Office Action of February 22, 2010, at page 6. Specifically, the Office asserts that, because the claims recite complex mixtures comprising proteins and/or peptides, it is asserted that a compound may interact with a majority or a minority of the proteins and/or peptides depending on the composition of the complex mixture used. Id. Thus, the Office asserts that "without reference to objective structural features common to the genus, it is not possible to determine what compounds fall within the claimed genus and what compounds do not, since the inability of the compound to interact with the majority of proteins and/or peptides in the sample depends upon the identity of the sample, which may vary." Id., at page 7. Claims 1, 6, 7, and 15 have been cancelled herein, rendering the rejection of these claims moot. Applicants respond further as follows.

Without agreeing that the language of the previously presented claims was in any way

indefinite (*e.g.*, the applicants do not agree that one of ordinary skill in the art would not know whether an isolation method using a binding compound and a certain complex mixture would fall within the scope of any previously presented claim), the applicants have cancelled claim 1, and added claim 17. New claim 17, from which amended claims 2-5, 13, and 14 depend, does not recite, "wherein said compound does not interact with the majority of said proteins and/or peptides." Therefore, at least the amended claims do not recite an element that renders the compound used in the method "depend[ent] upon the identity of the sample." Office Action, at page 7. For at least this reason, the applicants respectfully request the rejection of claims 2-5, 13, and 14 under 35 U.S.C. §112, second paragraph, be withdrawn.

35 U.S.C. §102

Claim 16 stands rejected under 35 U.S.C. §102(b) as assertedly being anticipated by Creighton, T.E., Proteins: Structures and Molecular Properties, 2nd Edition, W.H. Freeman and Company, New York, 1993; pages 10-20 and 31-41 (hereinafter "Creighton"). The Office asserts that Creighton discloses diagonal techniques for peptide purification in which peptides containing a particular amino acid are selectively isolated in two electrophoretic or chromatographic steps with an intervening modification step that alters the mobilities of modified peptides. Office Action of February 22, 2010, at page 7. The Office further seems to assert that the claim element, "chemically and/or enzymatically altering in a fraction from the first chromatographic step the compound present in at least one compound-interaction partner complex such that the altered compound-interaction partner complex elutes at a different elution time than the same non-altered compound-interaction partner complex in the same chromatographic separation" is the same as the modification step of Creighton (*i.e.*, covalent modification of specific amino acids in a peptide by iodacetic acid, cyclohexanedione, or trifluoroacetyl, maleyl, or dinitrophenyl groups). Id., at pages 7-9.

Claim 16 also stands rejected under 35 U.S.C. §102(b) as assertedly being anticipated by Cruickshank *et al.* (1974) Can. J. Biochem. 52:1013-7 (hereinafter "Cruikshank"). Office Action of February 22, 2010, at page 9. Specifically, the Office asserts that Cruikshank discloses isolation of tyrosyl- or histidyl-containing peptides *via* formation of FDNB-interaction partner complexes through reactions between FDNB and tyrosyl side chains, separation of the resulting

mixture by paper chromatography, subsequent modification of DNP by thiolysis, and isolation by a second paper chromatography step, wherein the chromatography steps were performed under identical conditions. Id., at pp. 9-10.

Applicants have cancelled claim 16, rendering both rejections of this claim under 35 U.S.C. §102(b) moot.

With respect to new claim 17, the applicants note that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. MPEP §2131; Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987). An asserted anticipating reference must show the identical invention *in as complete detail as is contained in the claim.* MPEP §2131. Neither Creighton nor Cruickshank can anticipate claim 17, or any of amended claims 2-5, 13, and 14 that depend therefrom, for at least the reason that neither reference discloses a molecule that specifically and stably interacts with at least one of the proteins and/or peptides in a complex mixture, wherein the specificity of the interaction is determined by secondary or tertiary structure of the protein or peptide. The non-specific binding of the molecules of Creighton and Cruickshank to amino acid side chains is not determined by secondary or tertiary structure of proteins and/or peptides; *i.e.*, the compounds of Creighton and Cruikshank interact with a primary structural element, to wit, particular amino acids.

Moreover, during patent examination, the Office must give claims their broadest reasonable interpretation that is consistent with the Specification *and consistent with the interpretation that those skilled in the art would reach.* MPEP §2111 (citing In re Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999)). A "specific" interaction is a common term of art in biochemistry that, with respect to proteins and peptides, defines an interaction that may be distinguished from other "non-specific" interactions. In biology, "specific" interaction has a particular meaning in many contexts that defines binding between a protein and/or peptide or class of proteins and/or peptides that share a common secondary or tertiary structure, such as an epitope or active site. See, *e.g.*, pages 320-321 of King, R.C. and Stansfield, W.D. A Dictionary of Genetics, Fifth Edition, Oxford University Press, Inc., New York, NY, 1997 (definition of "specificity") (Provided in attached Supplemental Disclosure Statement). This is clearly the definition of "specificity" that is used throughout the application, which one of ordinary skill in

the art would immediately recognize upon reading the application. See, *e.g.*, Specification, for example; at page 1, line 35, through page 2, line 5; page 5, lines 5-26; page 6, lines 22-33; page 23, line 29, through page 24, line 12; and Figs. 1-3. This definition of "specific" interaction is not inconsistent with the definition of "specific" binding provided at page 5, lines 21-24, of the Specification[1], particularly in view of page 2, lines 7-8, of the Specification, which recites, "the activity of drugs is due to the specific interaction with proteins influencing their biological activity."

Thus, under the definition of "specific interaction" that is used throughout the application, any binding compound that exhibits a binding specificity determined only by a single amino acid side chain reactive group cannot bind "specifically;" *i.e.*, because such a binding compound will bind to every one of such amino acid side chain reactive groups in a sample.

Tyrosyl-, histidyl-, and thiol-reactive compounds, as described by Creighton and Cruickshank, are not believed capable of specific interactions with proteins or peptides. A compound that exhibits specific binding may form a covalent bond with a protein or peptide through a tyrosyl, histidyl, or thiol side chain reactive group, but additional structural elements must determine the binding specificity. This is readily apparent to those of ordinary skill in the art, who would understand that tyrosyl-, histidyl-, and thiol-reactive compounds will necessarily react with every protein and peptide in a mixture that contains the tyrosyl, histidyl, or thiol group. The overly broad interpretation presented by the Office with respect to "specific interaction" in the recent Office Action (Id., at page 26) is entirely inconsistent with the interpretation that one of ordinary skill in the art would reach; that interpretation would require any chemical reaction between a compound and an amino acid to be "specific," and would render the entire Specification nonsensical. Thus, the interpretation of the term, "specific," as proposed by the Office with respect to the present application is not "consistent with the interpretation that those skilled in the art would reach," and cannot be correct. See, MPEP §2111.

New claim 18 cannot be anticipated by Creighton or Cruickshank, for at least the additional reason that neither reference discloses a compound comprising "a chemically reactive group by which the molecule and the at least one proteins and/or peptides may be cross-linked,

[1] "The binding of a compound to the target is specific, meaning that said compound binds to at

wherein the molecule comprises a chemical structure that binds to the at least one proteins and/or peptides, and wherein the chemically reactive group and the chemical structure are different."

New claim 19 cannot be anticipated by Creighton or Cruickshank, for at least the additional reason that neither reference discloses a compound "wherein the secondary or tertiary structure of the protein or peptide that determines the specificity of the interaction between the molecule and the protein or peptide is unknown."

New claim 20 cannot be anticipated by Creighton or Cruickshank for at least the additional reason that neither reference discloses a compound "wherein the at least one protein and/or peptide can only form molecule-interaction partner complexes with the molecule when the at least one protein and/or peptide are in a particular conformation."

For at least the foregoing reasons, the applicants respectfully submit the rejection under 35 U.S.C. §102(b) has been overcome.

35 U.S.C. §103

Claims 1-7 and 15 stand rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Creighton in view of US Patent 6,670,194 to Aebersold *et al.* (hereinafter "Aebersold"), and further in view of Beals *et al.* "Amino Acid Frequency," retrieved by the Office from http://www.teim.utk.edu/bioed/webmodules/aminoacid.htm (hereinafter "Beals"). Office Action of February 22, 2010, at p. 11.

The Office asserts that the compounds of Creighton possess the elements of compounds of the claimed methods, because "they are capable of reacting with a functionality present in the interacting peptides." Id., at page 12. The Office recognizes that Creighton does not disclose compounds that do not interact with the majority of proteins and/or peptides in a complex mixture, Id., at page 13, but asserts that "those of skill in the art at the time of the instant invention recognized the value in performing large-scale analyses of proteins in a so-called 'proteomics' approach." Id.

Aebersold is cited by the Office as evidence that the importance of proteins in biological processes was recognized, and as disclosing complex protein samples containing 100 different

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least one molecule in a complex mixture of molecules and not to other molecules."

proteins or more. Id. It is further asserted that "the methods of Aebersold et al. are therefore highly analogous to those of Creighton in that they involve selectively labeling certain protein groups (e.g., cysteines) and then isolating peptides that have been labeled. In particular, the affinity labeling reagent of Aebersold et al. may react with sulfhydryl groups, which is highly analogous to the labeling methods of Creighton et al." Id., at page 15.

The Office notes that amino acids exist in different frequencies in proteins, Id., at page 17, and further notes that the *digested* peptide samples of Aebersold contained a minority of peptides comprising cysteines. Id., at page 18 (emphasis added). The Office then states that "it would seem that the compounds of Creighton et al. would necessarily interact only with a **minority** of the peptides present in [complex mixtures such as blood]." Id. (Emphasis in original). Thus, the Office asserts,

> Consequently, when employing the various amino acid-reactive compounds taught by Creighton et al. (such as iodoacetic acid, cyclohexanedione, or trifluroacetyl, maleyl, or dinitrophenyl groups) in order to modify peptides in digested peptides from complex samples such as blood (as taught by Aebersold et al.), there is a strong scientific basis to believe that these compounds would covalently modify a minority of the peptides because they target amino acids that are relatively rare.

Id., at page 19.

In view of the foregoing, the Office concludes that it would therefore have been obvious "to perform the diagonal chromatography techniques of Creighton on complex samples such as blood, cells, tissues, and fractions thereof." Id. The Office further concludes that, "when taken together with the teachings of Aebersold et al. that the large-scale analysis of proteins expressed in a cell or tissue is important for completely describing a biological system, one would have been motivated to analyze samples containing as many proteins as possible in order to obtain as much information as possible about a particular biological system." Id., at page 16.

Claims 1, 6, 7, and 15 have been cancelled, rendering the 35 U.S.C. §103(a) rejection of these claims moot. With respect to new claim 17, from which amended claims 2-5, 13, and 14 now depend, the applicants respectfully assert that the cited combination of references cannot support a rejection under 35 U.S.C. §103(a) for at least the reason that none of the cited references teaches or suggests any molecule for use in presently claimed protein and/or peptide isolation methods that is capable of specific interaction.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there is to have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007). "Often, it will be necessary for a [fact finder] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." Id. Underlying the obvious determination is the fact that statutorily prohibited hindsight cannot be used. KSR, 127 S.Ct. at 1742.

Furthermore, to establish a *prima facie* case of obviousness, there must have been a reasonable expectation of success. MPEP §2143.02. There is no reasonable expectation of success in making a proposed modification to a reference when the resulting modification would be inoperable. Nor can a proposed modification to a reference change its principle of operation to support a rejection under 35 U.S.C. §103. MPEP §2143.01(VI). A claim is not obvious in view of a reference that teaches away from the claim, either by what it expressly or inherently teaches or fairly suggests. MPEP §§2144.02(VI) and 2145(X)(D)(2). A reference is said to "teach away" when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, "or would be led in a direction divergent from the path taken by the inventor." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

As set forth, *supra*, the applicants respectfully submit that the Office has given the claim element, "specific interaction," an impermissibly broad interpretation. Tyrosyl-, histidyl-, and thiol-reactive compounds, which are the only compounds taught or suggested by Creighton and Aebersold, are not capable of *specific* interactions with proteins or peptides. The compounds of Creighton are only able to react with particular amino acids. The compounds of Aebersold are only able to react with "protein reactive groups (PRGs)," whether naturally present on all of a particular amino acid or generated by enzyme activity. There is nothing in either reference that was applicable to purification or isolation of any molecule by other than the criteria that the molecule contains a particular amino acid at the time the invention was made without the use of

impermissible hindsight obtained from the present application.

New claim 18 cannot be made obvious by the cited references for at least the reason that none of the references teaches or suggests a molecule comprising "a chemically reactive group by which the molecule and the at least one proteins and/or peptides may be cross-linked, wherein the molecule comprises a chemical structure that binds to the at least one proteins and/or peptides, and wherein the chemically reactive group and the chemical structure are different." Such a molecule is outside the scope of the cited references, and a method using such a molecule for isolation of specific interaction partners of the molecule was not otherwise within "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention. KSR, 127 S. Ct. at 1742.

New claim 19 cannot be made obvious by the cited references, for at least the additional reason that none of the references discloses a compound "wherein the secondary or tertiary structure of the protein or peptide that determines the specificity of the interaction between the molecule and the protein or peptide is unknown." In fact, both Creighton and Aebersold rely on the fact that the chemical structure determining the binding interaction is known, either to obtain separation of all the proteins in a mixture, or to *a priori* deduce a particular interaction, respectively.

Likewise, new claim 20 cannot be made obvious by the cited references, for at least the additional reason that none of the references discloses a compound "wherein the at least one protein and/or peptide can only form molecule-interaction partner complexes with the molecule when the at least one protein and/or peptide are in a particular conformation."

Claim 13 stands rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Creighton in view of Aebersold, and further in view of Beals and US Patents 5,705,351 (to Sahasrabudhe; hereinafter "Sahasrabudhe") and 5,474,780 (to Chang; hereinafter "Chang"). Office Action of February 22, 2010, at page 22. The Office recognizes that Creighton does not disclose compounds which are drugs, Id., and asserts that Sahasrabudhe "provides evidence that fluro-2,4-dinitrobenzene is a drug" that can be used to "chemically treat cells for therapy of non-leukemic cancer" and cancer diagnosis. Id., at page 23. The Office further asserts that Chang "teaches that maleic anhydride is used as an ingredient in medical preparations for drug

delivery." Id. Thus, the Office concludes that in view of Sahasrabudhe and Chang, the compounds of Creighton are drugs. Id.

Applicants do not agree that either FDNB or maleic anhydride is a drug, or that Sahasrabudhe or Chang teach that either compound is a drug. However, claim 13 has been amended to depend from claim 17. Applicants respectfully assert that claim 17 is nonobvious for the reasons set forth, *supra*, as Beals, Sahasrabudhe, and Chang do not remedy the deficiencies of Creighton and Aebersold with respect to the claimed subject matter. Claim 13 is nonobvious for at least the reason that amended claim 13 incorporates each and every element of claim 17. Thus, the applicants respectfully request the rejection of claim 13 under 35 U.S.C. §103(a) be withdrawn.

Claim 14 stands rejected under 35 U.S.C. §103(a) as assertedly being unpatentable over Creighton in view of Aebersold, and further in view of Beals and GE Healthcare, "Fraction Collectors: Frac-950 and Frac-920," retrieved by the Office from http://www1.gelifesciences.com (hereinafter "GE Healthcare"). Office Action of February 22, 2010, at page 23. The Office recognizes that Creighton and Aebersold do not disclose pooling HPLC fractions to avoid elution overlap between different peaks, Id., and asserts that GE Healthcare demonstrates that it was known in the art "to adjust the size of collected fractions when performing chromatographic procedures in order to avoid re-mixing of proteins separated on the column." Id., at page 24. Applicants respectfully traverse the rejection.

Claim 14 is nonobvious, notwithstanding the Creighton, Aebersold, Beals, and GE Healthcare references for at least the reasons set forth, *supra*, with respect to claim 17. Beals and GE Healthcare do not remedy the deficiencies of Creighton and Aebersold with respect to the subject matter of claim 17, and claim 13 is nonobvious for at least the reason that amended claim 13 incorporates each and every element of claim 17.

Additionally, claim 14 has been amended to recite, "wherein multiple non-neighboring fractions obtained from the first chromatographic step are pooled prior to the second chromatographic step." The Office has asserted that claim 14 previously did not "recite or require pooling of non-neighboring fractions." Office Action, at page 27. GE Healthcare relates only to the pooling of single fractions, and does not concern the pooling of non-neighboring

fractions. The apparatus described in GE Healthcare uses peak fractionation that is "based on peak detection using slope or level sensing," Id., for example at page 3, and "two simple rotational movements," Id., at page 2, that do not provide for pooling non-neighboring fractions.

For at least the foregoing reasons, the applicants respectfully request the rejection of claim 14 under 35 U.S.C. §103(a) be withdrawn.

If questions remain after consideration of the foregoing, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted.

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Enclosure: Supplemental Information Disclosure Statement